

Supplemental Material

Lead and PCBs as Risk Factors for Attention Deficit Hyperactivity Disorder

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Supplemental Material, Table 1. Descriptions of behavioral tasks used in human studies examining the effects of environmental contaminants on cognitive domains affected in ADHD.

Auditory-Visual Learning Test (AVLT): The subject hears a list of 15 words repeated 5 times and is asked to recall the words after short and long-term delays. Impaired short-term recall suggests impaired verbal working memory.

California Verbal Learning Task – Children (CVLT-C): The subject hears a list of 15 words belonging to 3 semantic categories in repeated trials and is then asked to recall the words under conditions of short and long-term delay, interference, cueing, and recognition. Impaired immediate recall suggests impaired verbal working memory. Perseverative repetition of words already recalled on the same trial also suggests impaired working memory, but could also reflect attentional impairments.

Cambridge Neuropsychological Tests Automated Battery (CANTAB) Intra-dimensional-Extra-dimensional (ID-ED) shift test: A computerized analogue of the Wisconsin Card Sorting Test in which the subject learns by trial and error which of two shapes is correct. After a series of correct trials the contingencies are reversed and the other shape becomes correct. A series of reversal problems is presented, some including ID shifts in which new stimuli in the same dimension are introduced (a different set of shapes), and some including ED shifts in which stimuli in a dimension that was previously irrelevant are introduced (lines). A decrease in the number of problems completed during the testing session and perseverative responding after shifts both suggest impaired cognitive flexibility.

CANTAB Spatial Span (SpS): A visual-spatial analogue of the digit span task in which 10 randomly placed white squares appear on the computer screen one at a time. Then a subset of the squares change color (target boxes) and return to white. The subject is instructed to touch the boxes in the order they originally appeared. As with digit span, the number of boxes in the sequence increases across trials. An increase in touching boxes out of sequence (non-target errors) suggests impaired spatial working memory.

CANTAB Spatial Working Memory (SWM): The subject touches boxes on the computer screen to determine whether they contain a token. Tokens are moved to the right side of the screen to fill a container. A trial ends when the container is filled. An efficient search strategy involves remembering where previously searched tokens were found to avoid revisiting those boxes. Revisiting boxes suggests spatial working memory deficits.

CANTAB Stockings of Cambridge (SOC) Test: A computerized analogue of the Tower of London test in which the subject moves colored balls on the lower half of the computer screen to match the arrangement shown on the upper part of the screen. The object is to do this using the fewest possible moves. An efficient strategy is to plan the moves before beginning. Individuals that require more moves to solve the problem likely have impaired planning.

Choice Reaction Time (CRT): Different letters appear one at a time on a computer screen. The subject is instructed to respond (e.g., press a computer key) as quickly as possible when a previously specified target letter appears. Responding when the target letter is not present (errors of commission) suggests impaired response inhibition while omitting responses when the target letter is present (errors of omission) suggests impaired vigilance.

Continuous Performance Task (CPT): The subject responds as rapidly as possible to a rare target sequence (e.g., letter “X” when it is preceded by letter “A” but not by other letters) while inhibiting responses to non-target sequences. Similar to CRT in that errors of commission suggest impaired response inhibition while errors of omission suggest impaired vigilance. Increased reaction time for responses to the target sequence suggests impaired alertness.

Corsi Spatial Span: A visual-spatial analogue of the digit span task in which the subject taps blocks in the same order tapped by the examiner. Tapping out of sequence suggests spatial working memory impairments.

Differential Reinforcement of Low Rates of Responding (DRL): The subject is rewarded for the first response after a fixed interval of time has passed. A premature response resets the clock and delays reinforcement. Premature responding, shortened times between responses (inter-response times), and a decrease in rewards earned suggest impaired response inhibition.

Digit Cancellation: The subject crosses out target numbers (e.g., 3's and 7's) from random lists of numbers. Omission errors suggest a deficit in vigilance.

Digit Span: The subject recalls a random sequence of numbers in the order they were presented. Impaired number recall suggests verbal working memory deficits.

Kagan Matching Familiar Figures Visual Discrimination (VD) Test: The subject is asked to select from a group of stimuli the one that is identical to a previously specified target. Increased time to find the target suggests impaired alertness.

Mazes: The subject is asked to trace a series of mazes as quickly as possible without entering into blind alleys. The complexity of the mazes increases as the task progresses. A decrease in correct responses suggests planning deficits.

McCarthy Scales of Children's Abilities (MSCA): Composed of 18 subtests that assess various aspects of cognitive function. Includes verbal memory and numerical memory subtests which tap working memory function. The verbal memory tests assess the ability to recall strings of words, sentences, and a story. The numerical memory tests measure the ability to repeat strings of numbers, both forward and backward, as the strings get progressively longer. Impaired verbal and number recall suggests working memory deficits.

Mental Rotation: A series of individual letters are displayed on a computer screen. Letters are displayed either forwards or backwards (a mirror image) at either 0, 30, 60, 90 or 120 degrees from the vertical position. The subject is asked to indicate whether each letter is in a forward or backward position. While increased errors suggest poorer spatial reasoning, increased time to provide the correct answer suggests impaired alertness.

Pattern Memory: A subtest of the Neurobehavioral Evaluation System 2 (NES2) computerized test battery in which the subject is shown a series of different patterns composed of black and white squares, presented one at a time. After an interval, the subject is given trials in which three different patterns are presented simultaneously and the subject has to select the one that matches the patterns seen previously. A decrease in correct answers suggests non-verbal working memory impairments.

Rey-Osterrieth Complex Figure Test (ROCF): The subject is asked to copy a detailed abstract figure and then to reproduce it from memory. The subject is scored on measures including accuracy and organization. A decreased organizational score suggests planning deficits.

Seashore Rhythm Task (Seashore): The subject listens to pairs of tonal sequences and is asked to determine whether the sequences are the same or different. A decrease in correct answers suggests impaired non-verbal working memory.

Shape School Task: A task presented in the form of a large story book that includes phases to assess working memory, response inhibition, cognitive flexibility, and planning.

Simple Reaction Time Test (SRTT): The subject is asked to produce a response (e.g., push a button) as quickly as possible when a previously specified target stimulus is seen or heard. Increased reaction time suggests a deficit in alertness.

Sternberg Memory Task (Sternberg): The subject is shown sets of 1, 3, or 5 digits on a computer screen for 4 sec. each. Next, the subject is shown single digits and asked whether these match any of the digits seen previously. A decrease in correct answers suggests deficits in working memory. Increased reaction time suggests a deficit in alertness. Errors of commission suggest impaired response inhibition.

Stimulus Discrimination: A single object or letter is shown, followed by a screen with a string of objects or letters which contains the original object or letter. The subject is asked to locate the original stimulus. Increased reaction time suggests a deficit in alertness.

Story Recall: The subject is asked to recall verbatim a paragraph of a story (“How Mr. Lincoln Helped the Pig”) immediately after the story is told and then following a delay. Impaired immediate recall suggests a verbal working memory deficit.

Stroop Color-Word Test (Stroop): The subject is asked to name the color of ink that is used to print congruent and then incongruent color words (e.g., blue ink is used to print the word “blue” then it is later used to print “green”). An interference score is calculated with higher scores as well as longer time to reply suggesting impaired cognitive flexibility.

Tower of London (TOL) Test: In as few moves as possible, the subject is asked to move pre-stacked objects to match the configuration of objects in a model stack shown by the examiner. Poorer performance suggests planning deficits.

Trail Making Test –Part B (TMT-B): Circles containing letters and numbers are connected in ascending order while alternating between them (e.g., connect circle 1 to circle A to circle 2 to circle B...). Increased time to complete each problem suggest a cognitive flexibility deficit.

Underlining: A target pattern must be memorized and then underlined wherever it occurs on forms that are printed with series of different patterns. An increase in the number of target patterns that the subject fails to underline suggests impaired vigilance.

Visual Memory Span: Squares of different colors are shown on a screen. The squares are illuminated in a random sequence. The subject is asked to touch the squares in the order they were illuminated. Similar to Corsi Spatial Span. Impaired performance suggests a deficit with spatial working memory.

Visual Search: The subject is asked to locate boxes containing a predetermined combination of letters and dots from among several boxes on a screen that contain different combinations of letters and dots. A decrease in the number of correct answers suggests a problem with alertness, while commission errors suggest impaired response inhibition.

Wechsler Intelligence Scales for Children – Revised (WISC-R) – Digit Span and Arithmetic Subtests: Subtests in the WISC that assess working memory function. See **Digit Span** above. In the arithmetic subtest, a subject has to answer orally administered arithmetic questions while the answers are timed. A **freedom from distractibility score** can be computed by combining the results on the working memory subtests, with poorer scores suggesting verbal working memory impairments.

Wide Range Assessment of Memory and Learning (WRAML): Composed of a series of subtests that assess memory and learning. Working memory functions can be assessed in the sentence, story, picture, and memory subtests, as well as in the verbal learning, and verbal and symbolic working memory subtests. In the story memory test, the subject hears 2 stories and is asked to repeat each story immediately and after a 35-min delay. In the verbal learning test, the subject learns a list of either 13 or 16 words in 4 trials. In the verbal working memory test, the subject hears a list of words, and is asked to separate animal from non-animal words as well as to sequence the animal and non-animals according to their size. Verbal working memory impairments are suggested by poorer immediate recall.

Wisconsin Card Sorting Test (WCST): The subject is asked to infer the correct criterion (color, shape, or number) for sorting a set of symbol or picture cards based on feedback from the examiner indicating whether attempted sorts are correct or incorrect. After the subject correctly sorts the cards in a series of consecutive trials, the criterion is changed without warning. An increase of perseverative errors after a criterion change, in addition to decreases in the number of categories completed and conceptual level responses, suggest deficits in cognitive flexibility.

Supplemental Material, Table 2. Descriptions of behavioral tasks used in animal studies examining the effects of environmental contaminants on cognitive domains affected in ADHD.

5-Choice Serial Reaction Time Task (5-CSRT): The subject monitors 5 cue holes for a visual signal in one of the holes. The subject must then nose poke in the same hole in which the signal occurred. A variable delay can be interposed between trials. Omissions and responses in incorrect holes suggest vigilance deficits. Premature and perseverative responses suggest response inhibition deficits.

Differential Reinforcement of Low Rates of Responding (DRL): The subject is rewarded for the first response after a fixed interval of time has passed. A premature response resets the clock and delays reinforcement. Increased responding, decreased time between responses (inter-response time), and shorter delays before responding resumes after a reinforcer is delivered (post-reinforcement pause) suggest response inhibition deficits.

Delayed Spatial Alternation (DSA): The subject must alternate responses between two locations with delays interposed between each opportunity to respond. Increased errors suggest a working memory deficit. Premature responses suggest response inhibition deficits. Perseverating at an incorrect location could also reflect impaired response inhibition.

Discrimination Reversal Learning (Rev Lrn): One of two possible choices is consistently reinforced. Once the correct association is learned, the previously incorrect choice becomes the correct one (reversal). Choices can be based on spatial position (S) or non-spatial (NS) dimensions such as color or shape. Reversals can be intra-dimensional (e.g., red to green) or extra-dimensional (e.g., red to square). Increases in errors, including perseveration on the previously correct choice, and omissions after reversals suggest impaired cognitive flexibility.

Extinction (EXT): In this schedule, responding is never rewarded, which can ultimately result in a cessation (extinguishing) of responding. EXT schedules can alternate with other schedules during daily sessions (i.e., FI-EXT) or can follow a period of testing on a different schedule (i.e., FI, EXT). Increased responding and decreased inter-response times suggests response inhibition deficits.

Fixed Interval (FI): The subject is rewarded for the first response after a fixed interval of time has passed. Premature responses are neither rewarded nor penalized. Increased responding, decreased inter-response times, and shorter post-reinforcement pauses suggest response inhibition deficits.

Fixed Ratio-FI (FR-FI): FR and FI components are alternated within the same testing session. For FR, a reinforcer is delivered after a given number of responses (e.g., 5 responses:1 reward). Impaired transition between response strategies suggests cognitive flexibility deficits.

Fixed Ratio-Waiting for Reward (FR-Wait): The subject makes a given number of responses to receive a reward (FR component). Reinforcers then continue to be delivered at increasing intervals without any further action by the subject. However, when the subject does respond for the first time after the initial reward was issued, rewards are stopped and the FR component is reinstated to begin the next trial. Increased responding and responding sooner after the initial reward is issued suggest response inhibition deficits.

Minimum Response Duration: The subject holds a lever down for a pre-determined length of time in order to receive a reinforcer. Premature release of the lever is not rewarded. Shorter response durations suggest impaired temporal information processing.

Random Interval-Random Interval (RI-RI): Presses on two levers are reinforced after different intervals (e.g., lever 1 = 60 sec., lever 2 = 15 sec.). Reward intervals on the two levers are altered during the testing session to vary the relative reward density between levers. Efficient performance involves adjusting to respond more frequently on whichever lever has the shorter reward interval. Less efficient performance suggests cognitive flexibility deficits.

Repeated Acquisition-Performance (Repeat Acq-Perform): During each session, testing alternates between sets of performance trials, in which subjects respond to a stimulus with a 3-part response sequence that never varies, and sets

of acquisition trials, in which a new 3-part response sequence is learned. The new acquisition sequence remains the same during a daily testing session but changes in future sessions. A decrease in correct responses suggests impaired cognitive flexibility, while premature responding before the stimulus suggests a response inhibition deficit.

Signal Detection (Signal Det): Similar to 5-CSRT, a subject must monitor for and respond to a visual signal. The number of locations at which the signal can occur may vary between studies and variable delays can be interposed between trials. Also, a distractor (Distract, e.g., an olfactory cue) can be randomly provided to draw attention from the visual cue. Omissions and responses at an incorrect location suggest a vigilance deficit, while omissions in the presence of the distractor suggest a selective attention deficit. Premature responses suggest impaired response inhibition.

Variable Interval-DRL (VI-DRL): Similar to the FI schedule, the VI schedule rewards the first response after an interval of time has passed. However the interval varies around a mean value from trial-to-trial so the interval can not be precisely predicted. During each trial of a VI-DRL schedule, VI and DRL schedules run conjunctively so that several DRL components (e.g., 14 sec. each) must be successfully completed while time elapses on the longer VI schedule (e.g., average of 120 sec.) in order to receive a reinforcer. This typically generates a low but steady rate of responding. Increased responding and shorter inter-response times during the VI schedule suggest impaired response inhibition.
